## Phylogeny

EIF2AK3/PERK is classified within the eIF2α kinase (EIF2AK or eIF2K) family of the human kinome, a grouping based on sequence and functional similarities (axten2017proteinkinaser(pkr)–like pages 1-7, axten2017proteinkinaser(pkr)–like pages 19-24, english2022a(dis)integratedstress pages 19-21). This family also contains three other kinases that phosphorylate the eukaryotic initiation factor 2 alpha subunit (EIF2S1): GCN2 (EIF2AK4), PKR (EIF2AK2), and HRI (EIF2AK1) (axten2017proteinkinaser(pkr)–like pages 7-11, unknownauthors2014perkeif2alphakinase pages 15-19). The eIF2α kinase family belongs to the larger CMGC group of kinases (axten2017proteinkinaser(pkr)–like pages 24-28). Functional orthologs of PERK have been identified and characterized in model organisms, including mouse (*Mus musculus*), *Drosophila melanogaster*, and *Caenorhabditis elegans*, indicating evolutionary conservation of this ER stress response mechanism (donnelly2013theeif2αkinases pages 1-3, unknownauthors2015thefunctionalinterplay pages 39-43).

## Reaction Catalyzed

ATP + [EIF2S1 protein] = ADP + [phospho-EIF2S1 protein] (axten2017proteinkinaser(pkr)–like pages 1-7, axten2017proteinkinaser(pkr)–like pages 19-24, harding2012uncouplingproteostasisand pages 1-2).

## Cofactor Requirements

The catalytic activity of EIF2AK3/PERK requires a divalent cation cofactor, specifically Mg²⁺, which coordinates with ATP to facilitate phosphate transfer (johnson2023anatlasof pages 4-4, park2014regulationandfunction pages 100-105).

## Substrate Specificity

PERK phosphorylates its primary substrate, EIF2S1/eIF2α, at serine 51 (Ser51) (axten2017proteinkinaser(pkr)–like pages 15-19, axten2017proteinkinaser(pkr)–like pages 7-11). According to the priority source, PERK has a preference for proline-directed motifs, containing a proline residue adjacent to the phosphoacceptor site (johnson2023anatlasof pages 4-4). In contradiction, another source identified a peptide substrate for PERK that indicates a preference for arginine-rich sequences flanking the phosphorylation site (park2014regulationandfunction pages 100-105).

## Structure

EIF2AK3/PERK is a type I endoplasmic reticulum (ER) transmembrane protein (axten2017proteinkinaser(pkr)–like pages 1-7). Its architecture comprises three principal domains: an N-terminal stress-sensing domain located in the ER lumen, a single transmembrane segment, and a C-terminal kinase domain in the cytosol that executes its catalytic function (axten2017proteinkinaser(pkr)–like pages 1-7, donnelly2013theeif2αkinases pages 1-3). The crystal structure of the human PERK ER luminal domain has been determined (PDB ID: 4YZY), and crystal structures of the kinase domain bound to inhibitors show it in a DFG-in conformation (park2024ethnicvariationand pages 13-16, axten2017proteinkinaser(pkr)–like pages 15-19). Key regulatory features within the kinase domain include the activation loop, the C-helix (helix αG), and a hydrophobic spine, which are crucial for mediating conformational changes during activation (unknownauthors2015thefunctionalinterplay pages 39-43, donnelly2013theeif2αkinases pages 3-4). Autophosphorylation at Thr980 within the activation loop stabilizes both the loop and the C-helix, which is essential for kinase activity (donnelly2013theeif2αkinases pages 3-4, unknownauthors2015thefunctionalinterplay pages 39-43). Upon activation, PERK forms back-to-back dimers that can organize into linear arrays to facilitate trans-autophosphorylation (donnelly2013theeif2αkinases pages 3-4).

## Regulation

PERK is activated by ER stress, which triggers the dissociation of the ER chaperone BiP (GRP78) from its luminal domain, permitting PERK to homo-oligomerize and undergo trans-autophosphorylation (axten2017proteinkinaser(pkr)–like pages 1-7, donnelly2013theeif2αkinases pages 1-3, unknownauthors2011theeif2alphaphosphorylation pages 33-38). This autophosphorylation occurs on serine, threonine, and tyrosine residues, highlighting PERK as a dual-specificity kinase (axten2017proteinkinaser(pkr)–like pages 1-7, donnelly2013theeif2αkinases pages 3-4). Key activating phosphorylation sites include Thr980 in the activation loop and Tyr615, both of which are required for full kinase activity (donnelly2013theeif2αkinases pages 3-4, unknownauthors2015thefunctionalinterplay pages 39-43). Conversely, phosphorylation at Tyr561 in the juxtamembrane domain negatively regulates PERK by facilitating binding to the adaptor protein Nck1 via its SH2 domain, which delays PERK activation (unknownauthors2015nck1dependentregulationof pages 105-112). PERK signaling is also subject to negative feedback regulation. Downstream of PERK, the transcription factor ATF4 induces the expression of GADD34 (PPP1R15A) (hicks2023theppp1r15family pages 4-5, smedley2021theroleof pages 2-4). GADD34 functions as a regulatory subunit that recruits the catalytic subunit of protein phosphatase 1 (PP1) to specifically dephosphorylate phospho-eIF2α, which reverses the translational block and attenuates PERK signaling (english2022a(dis)integratedstress pages 2-4, hicks2023theppp1r15family pages 11-13).

## Function

PERK is a primary sensor of the unfolded protein response (UPR) and a key component of the integrated stress response (ISR) (axten2017proteinkinaser(pkr)–like pages 1-7, donnelly2013theeif2αkinases pages 1-3). It is expressed at high levels in secretory tissues, with the highest expression observed in the pancreas, specifically in beta cells and acinar cells (axten2017proteinkinaser(pkr)–like pages 7-11). The principal substrate of activated PERK is EIF2S1 (eIF2α) (axten2017proteinkinaser(pkr)–like pages 1-7). Phosphorylation of eIF2α at Ser51 attenuates global cap-dependent translation to reduce the client protein load on the ER (axten2017proteinkinaser(pkr)–like pages 1-7). Simultaneously, this event promotes the selective translation of certain mRNAs, such as that of the transcription factor ATF4 (axten2017proteinkinaser(pkr)–like pages 1-7, donnelly2013theeif2αkinases pages 1-3). ATF4 mediates an adaptive gene expression program by upregulating genes involved in stress mitigation, including *CHOP*, *GADD34*, *ATF3*, and *TRB3* (axten2017proteinkinaser(pkr)–like pages 7-11). PERK also phosphorylates and activates other substrates, including the transcription factor NRF2 to promote an antioxidant response and GSK-3β (unknownauthors2015nck1dependentregulationof pages 57-61, donnelly2013theeif2αkinases pages 3-4, unknownauthors2015thefunctionalinterplay pages 39-43). PERK plays essential roles in pancreatic β-cell viability and function, insulin synthesis and secretion, skeletal development, and postnatal growth (zhang2002theperkeukaryotic pages 10-10, unknownauthors2014perkeif2alphakinase pages 9-15). While its transient activation is cytoprotective, chronic PERK signaling can induce apoptosis through its downstream effectors ATF4 and CHOP (axten2017proteinkinaser(pkr)–like pages 11-15).

## Inhibitors

Experimental small-molecule inhibitors have been developed that are potent and selective for PERK (axten2017proteinkinaser(pkr)–like pages 15-19). These include the ATP-competitive kinase inhibitors GSK2606414 and GSK2656157, which bind to the kinase hinge region and exhibit nanomolar IC50 values (axten2017proteinkinaser(pkr)–like pages 15-19, axten2017proteinkinaser(pkr)–like pages 24-28). Other chemical classes of PERK inhibitors include indoline aminoquinazoline derivatives (axten2017proteinkinaser(pkr)–like pages 19-24). Experimental tools for PERK activation also exist, such as the Fv2E-PERK fusion protein, which can be selectively activated by the chemical dimerizer AP20187 (axten2017proteinkinaser(pkr)–like pages 11-15).

## Other Comments

Loss-of-function mutations in the *EIF2AK3* gene are the cause of Wolcott-Rallison Syndrome (WRS), a rare autosomal recessive disorder (axten2017proteinkinaser(pkr)–like pages 1-7, english2022a(dis)integratedstress pages 19-21). The clinical manifestations of WRS include neonatal- or early-onset insulin-dependent diabetes resulting from pancreatic β-cell failure, skeletal abnormalities, and growth retardation (axten2017proteinkinaser(pkr)–like pages 1-7, zhang2002theperkeukaryotic pages 10-10). The majority of pathogenic missense mutations associated with WRS are located within the kinase domain of PERK (park2024ethnicvariationand pages 9-13). Other genetic variants in PERK are associated with different diseases; certain alleles affecting the luminal domain are linked to tauopathies, while a specific haplotype known as PERK-B results in higher kinase activity and increased sensitivity to ER stress (park2024ethnicvariationand pages 9-13, ghura2024geneticknockinof pages 1-2). Pharmacological inhibition of PERK can produce pancreatic toxicity that mirrors the diabetic phenotype of WRS (axten2017proteinkinaser(pkr)–like pages 15-19).

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